

Attorney Docket No.: 330310.00102  
Customer No. 27160



U.S. Patent Application No.  
10/669,251

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re Application of:	:	
Leland SHAPIRO	:	Group Art Unit: 3736
Application No.: 10/669,251	:	Examiner: Not Yet Assigned
Filed: September 25, 2003	:	Confirmation No.: 3193
For: INHIBITORS OF SERINE PROTEASE ACTIVITY, METHODS AND COMPOSITIONS FOR TREATMENT OF NITRIC OXIDE INDUCED CLINICAL CONDITIONS	:	Atty. Dkt. No.: 330310.00102

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

February 8, 2005

**INFORMATION DISCLOSURE STATEMENT**

Dear Sir:

In compliance with the duty of disclosure under 37 C.F.R. §1.56 and in accordance with the practice under 37 C.F.R. §§1.97 and 1.98, the Examiner's attention is directed to the documents listed on the enclosed Forms PTO/SB/08A and PTO/SB/08B. Please note that these documents were all considered in related application 09/518,097, filed March 3, 2000; now U.S. Patent No. 6,489,308, issued December 3, 2002. For the convenience of the Examiner a partial copy of the above patent with the listed references is enclosed. The citation numbers have been marked on the patent for ease of comparison.

**FORMAL MATTERS**

In accordance with 37 C.F.R. § 1.97(b)(3), since a first Official Action on the merits of the subject application has not yet been issued, neither a certificate, petition nor payment of a fee is believed to be required for this Information Disclosure Statement. However, the Commissioner is hereby

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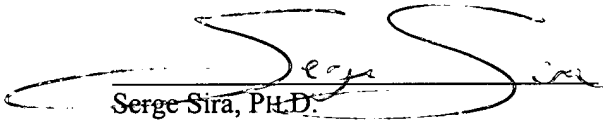
authorized to charge any fee which may be required in connection with this paper to Deposit Account No.  
50-1710.

CONCLUSION

It is respectfully requested that the above information be considered by the Examiner and that a copy of the enclosed Forms PTO/SB/08A and PTO/SB/08B be returned indicating that such information has been considered.

Applicant's undersigned attorney may be reached in our Washington, D.C. office by telephone at (202) 625-3500. All correspondence should continue to be directed to our address given below.

Respectfully submitted,

  
Serge Sira, Ph.D.  
Attorney for Applicant  
Registration No. 39,445

Patent Administrator  
KATTEN MUCHIN ZAVIS ROSENMAN  
525 West Monroe Street, Suite 1600  
Chicago, Illinois 60661-3963  
(202) 625-3500



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## INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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### Complete if Known

Application Number	10/669,251
Filing Date	September 25, 2003
First Named Inventor	Leland SHAPIRO
Art Unit	3736
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### U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No. <sup>1</sup>	Document Number	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		Number-Kind Code <sup>2</sup> (if known)			
	1	US- 4,021,472 A	05/1977	Fujii et al.	
	2	US- 4,051,842 A	10/1977	Hazel et al.	
	3	US- 4,140,122 A	02/1979	Kuhl et al.	
	4	US- 4,224,342 A	09/1980	Fujii et al.	
	5	US- 4,283,418 A	08/1981	Fuji et al.	
	6	US- 4,310,533 A	01/1982	Uegai et al.	
	7	US- 4,383,529 A	05/1983	Webster	
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	10	US- 4,668,504 A	05/1987	Kahan et al.	
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	18	US- 4,843,094 A	06/1989	Imaki et al.	
	19	US- 4,889,723 A	12/1989	Kim et al.	

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		Country Code <sup>3</sup> Number <sup>4</sup> Kind Code <sup>5</sup> (if known)				
	20	WO 94/07525	04/1994			
	21	WO 95/28422	10/1995			
	22	WO 95/34538	12/1995			
	23	WO 96/12021	04/1996			
	24	WO 96/14067	05/1996			
	25	WO 97/03679	02/1997			

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	26	US- 4,931,279 A	06/1990	Bawa et al.	
	27	US- 4,963,654 A	10/1990	Katunuma	
	28	US- 5,004,612 A	04/1991	Kim et al.	
	29	US- 5,077,428 A	12/1991	Imaki et al.	
	30	US- 5,110,602 A	05/1992	Kim et al.	
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	32	US- 5,166,134 A	11/1992	Lezdey et al.	
	33	US- 5,175,253 A	12/1992	Fallon et al.	
	34	US- 5,214,191 A	05/1993	Kirschenheuter et al	
	35	US- 5,216,022 A	06/1993	Oleksyszyn et al.	
	36	US- 5,240,956 A	08/1993	Kirschenheuter et al	
	37	US- 5,247,084 A	09/1993	Imaki et al.	
	38	US- 5,399,346 A	03/1995	Anderson et al.	
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	45	WO 97/09346	03/1997			
	46	WO 97/09347	03/1997			
	47	WO 97/10222	03/1997			
	48	WO 97/10231	03/1997			
	49	WO 97/21690	06/1997			
	50	WO 97/24339	07/1997			

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	51	US- 5,486,470 A	01/1996	Darke et al.	
	52	US- 5,489,593 A	02/1996	Palmer et al.	
	53	US- 5,504,094 A	04/1996	Nakane et al.	
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	61	US- 5,604,201 A	02/1997	Thomas et al.	
	62	US- 5,610,140 A	03/1997	Goodfellow et al.	
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	64	US- 5,614,555 A	03/1997	Nakai et al.	
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	66	US- 5,618,792 A	04/1997	Gyorkos et al.	
	67	US- 5,622,984 A	04/1997	Nakai et al.	
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	70	WO 97/31937	09/1997			
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First Named Inventor	Leland SHAPIRO
Art Unit	3736
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	76	US- 5,663,416 A	09/1997	Kirschenheuter et al	
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	78	US- 5,700,779 A	12/1997	Goodfellow et al.	
	79	US- 5,710,026 A	01/1998	Sprecher	
	80	US- 5,712,117 A	01/1998	Sprecher	
	81	US- 5,747,645 A	05/1998	Sprecher	
	82	US- 5,750,506 A	05/1998	Goodfellow et al.	
	83	US- 5,759,548 A	06/1998	Bathurst et al.	
	84	US- 5,780,009 A	07/1998	Karatzas et al.	
	85	US- 5,798,442 A	08/1998	Gallant et al.	
	86	US- 5,801,148 A	09/1998	Gyorkos et al.	
	87	US- 5,804,594 A	09/1998	Murad	
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	95	WO 98/06417	02/1998			
	96	WO 98/09206	03/1998			
	97	WO 98/20034	05/1998			
	98	WO 98/21186	05/1998			
	99	WO 98/22098	05/1998			
	100	WO 98/22619	05/1998			

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	101	US- 5,861,380 A	01/1999	Gyorkos et al.	
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	105	US- 5,874,585 A	02/1999	Gyorkos et al.	
	106	US- 5,891,852 A	04/1999	Gyorkos et al.	
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	226	US- 5,376,655 A	12/1994	Imaki et al.	
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	112	WO 98/23565	06/1998			
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	115	WO 98/49190	11/1998			
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	118	WO 98/56821	12/1998			
	119	WO 97/41231	08/1999			
	120	WO 99/43308	09/1999			
	121	WO 00/52034	09/2000			

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				Application Number	10/669,251
				Filing Date	September 25, 2003
				First Named Inventor	Leland SHAPIRO
				Art Unit	3736
				Examiner Name	Not Yet Assigned
Sheet	7	of	17	Attorney Docket Number	330310.00102

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	122	Aoki H, Akaike T, Abe K, Kuroda M, Arai S, Okamura R, Negi A, Maeda H. Antiviral effect of oryzacystatin, a proteinase inhibitor in rice, against herpes simplex virus type I in vitro and in vivo. Antimicrob Agents Chemother Apr. 1995; 39(4):846-9.	
	123	Auerswald et al., "Recombinant leech-derived trypsin inhibitor: construction, production, protein chemical characterization and inhibition of HIV-1 replication", Biol Chem Hoppe Seyler, 375(10):695-703 (1994).	
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	125	Beal, M.F., "Mitochondria, Free Radicals, and Neurodegeneration", Curr. Opin. Neurobiol., 1996, 6, 661-666.	
	126	Bjorck L, Grubb A, Kjellen L. Cystatin C, a human proteinase inhibitor, blocks replication of herpes simplex virus. J Virol Feb. 1990;64(2):941-3.	
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				Filing Date	September 25, 2003
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	132	Flaitz CM, Hicks MJ. "Molecular piracy: the viral link to carcinogenesis." Oral Oncol Nov. 1998;34(6):448-53.	
	133	Griffin, William C., "Calculation of HLB Values of Non-Ionic Sufactants", [H. L. B.--The Hydrophilic-Lipophilic Balance], J. Soc. Cos. Met. Chem., vol. 5, p. 249 (1954).	
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	135	Inocencio et al., "Endoprotease activities other than furin and PACE4 with a role in processing of HIV-1 gp160 glycoproteins in CHO-K1 cells", J Biol Chem, 272(2):1344-8 (1997).	
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	139	Kido H, Niwa Y, Beppu Y, Towatari T. Cellular proteases involved in the pathogenicity of enveloped animal viruses, human immunodeficiency virus, influenza virus A and Sendai virus. Adv Enzyme Regul 1996;36:325-47.	
	140	Best, P.J.M., et al., Arterioscler Thromb Vasc Biol 1999, 19, 14.	
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				First Named Inventor	Leland SHAPIRO
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	142	Meylan et al., "HIV infectivity is not augmented by treatment with trypsin, Factor Xa or human mast-cell tryptase", AIDS, 6(1):128-30 (1992).	
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	144	Molle W. et al. in J Immunol 1997, 159, 3555.	
	145	Morel, J. B. and Dangle, J.L., Cell Death Differ 1997, 4, 67 1.	
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	148	Pellegrini A, Thomas U, Franchini M, Stockli M, Klauser S, Hunziker P, von Fellenberg R. Identification of an aprotinin antiviral domain. FEBS Lett May 16, 1994;344(2-3):261-5.	
	149	Schwartz, et al., "Antiviral activity of the proteasome on incoming human immunodeficiency virus type I", J Virol, 72(5):3845-50 (1998).	
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	151	Szeghy G, Kenyeres B. On the therapy of herpes simplex keratitis with heparin and trypsin. [Article in German] Klin Monatsbl Augenheilkd 1968; 153(6):827-30.	

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				Application Number	10/669,251
				Filing Date	September 25, 2003
				First Named Inventor	Leland SHAPIRO
				Art Unit	3736
				Examiner Name	Not Yet Assigned
Sheet	10	of	17	Attorney Docket Number	330310.00102

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	152	Cilberto et al., 1985, Cell, 41:531-540.	
	153	Dery O. and Bunnett, N.W. Biochem Soc Trans 1999, 27, 246-254.	
	154	Altieri, D.C. J Leukoc Biol 1995, 58, 120-127.	
	155	Dery, O. et al. Am J Physiol 1998, 274, C1429-C1452.	
	156	Patel R. P., et al. in Biochim Biophys Acta 1999, 1411, 385-400.	
	157	Lowenstein, C. J. and Snyder, S. H. in Cell 1992, 70, 705-707.	
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	159	Kirkeboen, K.A. and Strand, O.A. in Acta Anaesthesiol Scand 1999, 43, 275.	
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	161	Lowenstein C. J. et al. in Proc. Natl. Acad. Sci. USA, 1993, 90, 9730.	

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				Filing Date	September 25, 2003
				First Named Inventor	Leland SHAPIRO
				Art Unit	3736
				Examiner Name	Not Yet Assigned
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	162	Nathan, C. in FASEB J. 1992, 6, 3501.	
	163	Rehman, A. et al. in Br J Pharmacol, 1997, 122, 1702.	
	164	Pryor, W. A. et al., in Chem Biol Interact 1985, 54, 171.	
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	167	Heck, D. E. et al., in J. Biol. Chem. 1990, 267, 21277.	
	169	McCall, T.B. et al., in Biochem. Biophys. Res. Commun. 1992, 186, 680.	
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	171	Goureau, O. et al., in Proc. Natl. Acad. Sci. U.S.A. 1993, 90, 4276.	

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	172	Schini et al. in Circ Res 1994, 74, 24.	
	173	Meki, A. R. et al. in Toxicon 1998, 36, 18519.	
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	176	Sambrook, Fritsch & Maniatis, Molecular Cloning: A Laboratory Manual, Second Edition 1989, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y.	
	177	Remington's Pharmaceutical Sciences, 1990, p. 1519-1675, Gennaro, A.R., ed., Mack Publishing Company, Easton, PA.	
	178	Langer, R., Nature, 1998, 392, 5.	
	179	Budavari, Susan (Editor), "The Merck Index", An Encyclopedia of Chemicals, Drugs, and Biologicals; Merck & Co., Inc., 11th edition.	
	180	Merrifield, R.B., "Solid Phase Peptide Synthesis. I. The Synthesis of a Tetrapeptide", 1963, J. Am. Chem. Soc., (85):2149.	
	181	Animal Cell Culture, R.I. Freshney, ed. 1986, IRL Press, Oxford.	

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	182	Scharpe et al., "Protease and their inhibitors: today and tomorrow", 1991, Biochimie, 73(1):121-126.	
	183	Kido et al., "A novel membrane-bound serine esterase in human T4+ lymphocytes immunologically reactive with antibody inhibiting syncytia induced by HIV-1. Purification and characterization", J Biol Chem., 1990, 265(35):21979-85.	
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	188	McNeely et al., "Secretory leukocyte protease inhibitor: a human saliva protein exhibiting anti-human immunodeficiency virus 1 activity in vitro", 1995, J Clin Invest, 96(1):456-64.	
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	190	Vollenweider, et al., "Comparative cellular processing of the human immunodeficiency virus (HIV-1) envelope glycoprotein gp160 by the mammalian subtilisin/kexin-like convertases", 1996, Biochem. J., 314 (Pt2):521-32.	
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				First Named Inventor	Leland SHAPIRO
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				Examiner Name	Not Yet Assigned
Sheet	14	of	17	Attorney Docket Number	330310.00102

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	192	Decroly, et al., "Identification of the paired basic convertases implicated in HIV gp160 processing based on in vitro assays and expression in CD4(+) cell lines", 1996, J Biol Chem, 271(48):30442-50.	
	193	Moulard, et al., "Kex2p: a model for cellular endoprotease processing human immunodeficiency virus type 1 envelope glycoprotein precursor", Eur J Biochem, 1994, 225(2):565-72.	
	194	Avril, et al., "Identification of the U-937 membrane-associated proteinase interacting with the V3 loop of HIV-1 gp120 as cathespin G", FEBS Lett, 1994, 345(1):81-6.	
	195	Harvima et al., "Separation and partial characterization of proteinases with substrate specificity for basic amino acids from human MOLT-4 T lymphocytes: identification of those inhibited by variable-loop-V3 peptides of HIV-1 (human immunodeficiency virus-1) envelope glycoprotein", 1993, Biochem J, 292 (Pt 3):711-8.	
	196	Bourinbaiar, et al., "Acrosin inhibitor, 4'-acetamidophenyl 4-guanidinobenzoate, an experimental vaginal contraceptive and anti-HIV activity", Contraception, 1995, 51(5):319-22.	
	197	Bristow, et al., "Inhibition of HIV-1 by modification of a host membrane protease", 1995, Int Immunol, 7(2):239-49.	
	198	Bukrinskaia et al., "Inhibition of HIV reproduction in cultured cells using proteolysis inhibitors", 1989, Vopr Virusol, 34(1):53-5.	
	199	Bourinbair, et al., "Effect of serine protease inhibitor, N-alpha-tosyl-L-lysyl-chloromethyl ketone (TLCK), on cell-mediated and cell-free HIV-1 spread", Cell Immunol, 1994, 155(1):230-6.	
	200	Turpin et al., "Human immunodeficiency virus type-1 (HIV-1) replication is unaffected by human secretory leukocyte protease inhibitor", 1996, Antiviral Res, 29(2-3):269-77.	
	201	Kennedy et al., "Submandibular salivary proteases: lack of a role in anti-HIV activity", 1998, J Dent Res, 77(7):1515-9.	

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				<b>Application Number</b>	10/669,251
				<b>Filing Date</b>	September 25, 2003
				<b>First Named Inventor</b>	Leland SHAPIRO
				<b>Art Unit</b>	3736
				<b>Examiner Name</b>	Not Yet Assigned
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	202	Premack, B.A. et al., "Chemokine Receptors: Gateways to Inflammation and Infection", 1996, Nature Medicine 2:1174-1178.	
	203	Zhirnov O.P. et al., "Antiviral activity of proteinase inhibitors in cultured cells infected with alpha-viruses", Mol Gen Mikrobiol Virusol, 1985, (12):30-6.	
	204	Chesnokova N.B. et al., "Antiproteases in herpetic keratitis", Metab Pediatr Syst Ophthalmol, 1986;9(1):593-6.	
	205	Adelman S.F. et al., "Protease inhibitors suppress fibrinolytic activity of herpesvirus-transformed cells", J Gen Virol, 1982, 60(Pt 1):15-24.	
	206	Chesnokova N.B. et al., "Main proteolytic inhibitors in ocular herpes", Vopr Med Khim, 1981, 27(5):663-5.	
	207	Sharpstone D. et al., "Faecal alpha 1 antitrypsin as a marker of gastrointestinal disease in HIV antibody positive individuals", Gut, 1996, 38(2):206-10.	
	208	Patel et al., "The Role of Protease Drug During Apoptosis", 1996, FASEB J, 10(5):587-597.	
	209	Estaquier J., "Fas-mediated apoptosis of CD4+ and CD8+ T cells from human immunodeficiency virus-infected persons: differential in vitro preventive effect of cytokines and protease antagonists", 1996, Blood, 15;87(12):4959-66.	
	210	Shimizu, T. et al., "DNA Fragmentation induced by Protease Activation in P53-null Human Leukemia HL60 Cells Undergoing Apoptosis Following Treatment with the Topoisomerase I Inhibitor Camptothecin: Cell-Free System Studies", 1996, Exp Cell Res, 1:226(2):292-301.	
	211	Glynn et al., "Apoptosis induced by HIV Infection in H9 T Cells is Blocked by ICE-Family Protease Inhibition but not by a FAS(CD95) Antagonist", 1996, J. Immunol, 1; 157(7):2754-2758.	

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				Application Number	10/669,251
				Filing Date	September 25, 2003
				First Named Inventor	Leland SHAPIRO
				Art Unit	3736
				Examiner Name	Not Yet Assigned
Sheet	16	of	17	Attorney Docket Number	330310.00102

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	212	Ooka, T., et al., "Protective effects of human uninary trypsin inhibitor against trypsin-induced relaxation in rat aorta", Crit care Med, 1996, 24(11): 1903-1907.	
	213	Novradovsky, A., et al., "Endothelial Nitric Oxide Synthase as a Potential Susceptibility Gene in the Pathogenesis of Emphysema in alpha1-Antitrypsin Deficiency", 1999, Am J Respir Cell Mol Biol, 1:20(3):441-447.	
	214	Cordiali Fei et al., "Behavior of several `progression markers` during the HIV-Ab seroconversion period. Comparison with later stages", 1992, J Biol Regul Homeost Agents, 6(2):57-64.	
	215	Lima et al., "Mucosal injury and disruption of intestinal barrier function in HIV-infected individuals with and without diarrhea and cryptosporidiosis in northeast Brazil", 1997, Am J Gastroenterol, 92(10):1861-6.	
	216	Banfi et al., "Tumor-associated trypsin inhibitor in induced and acquired immunodeficiency. Studies on transplanted and HIV-infected patients", 1991, Scand J Clin Lab Invest 51, Suppl, 207:55-8.	
	217	Deam et al., "Alpha 1-antitrypsin phenotypes in homosexual men", 1989, Pathology, 21(2):91-2.	
	218	Pezzilli et al., "Serum pancreatic enzymes in HIV-seropositive patients", Dig Dis Sci, 1992, 37(2):286-8.	
	219	Tang et al., "Inactivation of HIV-1 by trypsin and its use in demonstrating specific virus infection of cells", 1991, J Virol Methods, 33(1-2):39-46.	
	220	Glozman, "Immunologic functions of enzyme therapy of patients with orchiepidymitis", 1990, Antibiot. Khimioter, 35(7):50-52.	
	221	Franzusoff, et al., "Biochemical and genetic definition of the cellular protease required for HIV-1 gp160 processing", 1995, J Biol Chem, 270(7):3154-9).	

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				Filing Date	September 25, 2003
				First Named Inventor	Leland SHAPIRO
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	222	Gu et al., "Furin is important but not essential for the proteolytic maturation of gp160 of HIV-1", FEBS Lett. 1995, 365(1):95-7.	
	223	Bukrinskaia A.G., "Suppression of rotavirus SA-11 reproduction by protease inhibitors in cell culture", Vopr Virusol, 1987, 32(1):71-4.	

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